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(54) Title: A NEW COMPOSITION

(57) Abstract

The invention relates to a composition comprising a first component (a) which is *(R)*-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, the preparation thereof, pharmaceutical formulations containing said composition, use of and a method of treatment of affective disorders such as mood disorders and anxiety disorders with said composition as well as a kit containing said composition.

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A NEW COMPOSITION

Field of the Invention

The present invention relates to a composition which comprises a first component (a) which is *(R)*-3-*N*,*N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof. The present invention also relates to a process for the preparation of the inventive composition, pharmaceutical formulations containing said composition and to the use of said composition either by concomitant administration or by separate administration as an improvement of the treatment of affective disorders such as depression, anxiety, obsessive compulsive disorder (OCD), etc.

Background of the Invention

Today, it is generally considered that antidepressants take 2-4 weeks to reach full clinical effect. In contrast, the side effects occur immediately. Thus, slow onset of action of antidepressants leads to a vulnerable period for patients in which they experience the side effects, but not the therapeutic effects of drugs. There is often a heavy burden on the treating physician to persuade the patient to continue with the treatment during this period. Furthermore, in suicidal patients, as the onset of action is gradual, initiative may be regained without the experiencing of full reversal of symptoms, leaving a window of risk for suicide and a frequent requirement for hospitalization. An antidepressant with fast onset of action would not only be beneficial due to the faster symptom reduction, but would also be more acceptable to patients and physicians and reduce the need for and duration of hospitalization. The same long period to reach full clinical effect has been shown in the treatment of other affective disorders such as anxiety and OCD.

Prior art

In WO 96/33710 is disclosed that the compound *(R)*-5-carbamoyl-8-fluoro-3-*N,N*-dicyclobutylamino-3,4-dihydro-2*H*-1-benzopyran which has high affinity to 5-HT receptors and antagonizes 5-HT_{1A} mediated responses induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors.

Summary of the Invention

The present invention is directed to a new composition comprising of a first component (a) which is the specific 5-HT_{1A} antagonist *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, which is a 5-HT reuptake inhibitor. Said composition attains a faster onset of action and consequently, provides a more efficacious treatment of the patients suffering from affective disorders, particularly depression.

It has been shown in animal studies that acute administration of selective 5-HT reuptake inhibitors (SSRIs) decreases the electrical impulse propagation in 5-HT neurones via a negative feedback reaction probably mediated by collateral 5-HT axons releasing 5-HT in raphé nuclei. By inhibiting the somatodendritic 5-HT_{1A} autoreceptors in the raphé nuclei the selective antagonists counteract the decrease in propagetion caused by 5-HT reuptake inhibitors. This indicates that a selective blockade of somatodendritic autoreceptor i.e. 5-HT_{1A} antagonist may have a clinical potential to improve the efficacy of 5-HT reuptake inhibitors (SSRIs) and offer a new rationale for rapid onset of effect in the treatment of affective disorders, for instance the antidepressant actions.

The compound *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299) disclosed herein is described in J. Pharmacolog. Exp. Ther., 283, 216-225, (1997), as a selective 5-HT_{1A} receptor antagonist.

(R)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate possesses a high affinity to the specific subgroup of 5-HT_{1A} receptor in CNS and acts as an antagonist on that 5-HT_{1A} receptor, and as well show favourable bioavailability after oral administration.

1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt, and/or solvate thereof, is a 5-HT reuptake inhibitor (SSRI). 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile in the racemic form is known as citalopram, which is commercially available. The enantiomer (+)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile disclosed herein, is described in US 4,943,590.

Pharmaceutically acceptable salts of 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile in the racemic or enantiomeric forms may be hydrochlorides, hydrobromides, maleates, tartrates, acetates, oxalates, fumarates etc. and are also included in the inventive composition. Also solvate forms such as the hydrate and hemihydrate are included.

The composition according to the present invention may exist in one pharmaceutical formulation comprising the component (a) and component (b), or in two different pharmaceutical formulations, one for component (a) and one for component (b). The pharmaceutical formulation may be in the form of tablets or capsules, powders, mixtures, solutions or other suitable pharmaceutical formulation forms such as patches and nasal formulations.

The composition of the present invention can be prepared such that component (a) is incorporated into the same pharmaceutical formulation as component (b) by e.g. mixing in a conventional way.

The present invention also includes a method of improving the onset of therapeutic action by concomitant administration of a composition comprising of *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof.

A further embodiment of the present invention is a kit containing a dosage unit of *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, optionally with instructions for use.

Pharmaceutical formulations

According to the present invention the compounds in the composition will normally be administered orally, rectally, transdermally, nasally or by injection, in the form of pharmaceutical formulations comprising the active ingredients in a pharmaceutically acceptable dosage form . The dosage form may be a solid, semisolid or liquid formulation. Usually the active substances will constitute between 0.1 and 99% by weight of the formulation, more specifically between 0.5 and 20% by weight for formulations intended for injection and between 0.2 and 50% by weight for formulations suitable for oral administration.

The pharmaceutical formulation comprises the active ingredients, optionally in association with adjuvants, excipients e.g. diluents, and/or inert carriers.

To produce pharmaceutical formulations of the composition of the invention in the form of dosage units for oral application, the selected compounds may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatin or polyvinylpyrrolidone, disintegrants e.g. sodium starch glycolate, cross-linked PVP and cross-caramellose sodium; a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and an antisticking agent such as talc or colloidal silicon dioxide, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a polymer known to the man skilled in the art e.g. HPMC, HC or other cellulose derivatives or PVP, wherein the polymer is dissolved in water or a readily volatile organic solvent or mixture of organic solvents. Alternatively, the tablets can be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Dyestuffs may be added to these coatings for instance in order to readily distinguish between tablets containing different active substances or different amounts of the active compounds.

For the formulation of soft gelatin capsules, the active substances may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatin capsules may contain granules of the active substances using any of the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives, plasticizers, polyetheneglycol, waxes, lipids or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatin capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substances in a mixture with a neutral fatty base, or gelatin rectal capsules comprising the active substances in admixture with vegetable oil or paraffin oil. Liquid formulations for oral application may be in the form of

solutions, syrups or suspensions, for example solutions containing from about 0.2% to about 20% by weight of the active substances herein described, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid formulations may contain colouring agents, flavouring agents, saccharin and carboxymethyl-cellulose as a thickening agent or other excipients known to a person skilled in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substances, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the active compounds in the composition of the invention in therapeutic treatment of humans are about 0.01-100 mg/kg bodyweight for peroral administration and 0.001-100 mg/kg bodyweight for parenteral administration. The daily doses of the active ingredient *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate may very well differ from the daily doses of the active ingredient 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of free the base, or a pharmaceutically acceptable salt and/or solvate thereof but the doses can also be the same for both of the active ingredients.

Medical and Pharmaceutical Use

In a further aspect the present invention provides the use of the composition comprising a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base,

or a pharmaceutically acceptable salt and/or solvate thereof, and the use in the treatment of 5-hydroxytryptamine mediated disorders, such as affective disorders. Examples of affective disorders are disorders in the CNS such as mood disorders (depression, major depressive episodes, dysthymia, seasonal affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders (disorders of impulse control, trichotellomania) and sleep disorders. Other disorders in the CNS such as eating disorders (obesity, anorexia, bulimia), premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders (age associated memory impairment, presenile and senile dementia such as Alzheimer's disease), pathological aggression, schizophrenia, endocrine disorders (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain and hypertension may also be treated with the combination described herein. Examples of other hydroxytryptamine mediated disorders are urinary incontinence, vasospasm and growth control of tumors (e g lung carcinoma) and it may be possible to treat those with the combination described herein as well.

Pharmacology

Potentiation of the 5 HT_{1A} autoreceptor blocking effekt of 5-HT of citalopram by using of *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299).

Materials and methods

Animals

The studies were carried out in male Sprague-Dawley rats (290-450g; B&K Universal, Sollentuna, Sweden). The animals were housed for at least 3 weeks after arrival until used in the experiments.

Methods

The studies were carried out by means of intra-cerebral microdialysis in awake rats. To assess any putative regional differences between dorsal and median rapheinnervated 5-HT projection areas, dialysis probes were simultaneously implanted both into the frontal cortex (FCx) and dorsal hippocampus (DH).

Microdialysis

The rats were anaesthetised with a mixture of ketamine HCl (67 mg/kg intraperitoneal (IP); Ketalar®, Park-Davis) and xylazine HCl (13 mg/kg IP; Rompun®, Bayer-Leverkusen). U-shaped microdialysis probes (total dialysis fibre length 4 mm, OD 220μm) were stereotaxically implanted in the frontal cortex (FCx) and dorsal hippocampus (DH); probe tips at AP +3.5, ML -3.0, DV -4.2 and -4.3, ML +2.5, DV -4.2, respectively, *vs.* bregma and dura surface (Paxinos, et al, in The Rat Brain in Stereotaxic Coordinates, 2nd Ed., Academic Press, San Diego (1996)). The microdialysis studies were performed in conscious animals after a 40-48 h recovery period, during which they were kept individually. Food and water were allowed *ad libitum* in the plastic cages subsequently used in the experimental sessions. On the day of the experiment, the probe inlets were connected to a syringe perfusion pump (CMA/100; CMA Microdialysis AB, Sweden), delivering artificial CSF (Hjorth, S., J. Neurochem. 60:776-779 (1993)) at a speed of 1.3μl/min. Twenty-min dialysate fractions were collected from the probe outlet tubing, and immediately analysed for 5-HT and 5-HIAA by standard HPLC-EC methods. After the perfusion was commenced, a period of 2-3 h was allowed to establish stable baseline dialysate levels of 5-HT, prior to drug treatment(s). Two groups of rats were injected with citalopram (5.0 mg/kg SC) at time zero. 60 minutes later, NaCl (control) was given to one of the groups and NAD 299 (0.3 mg/kg SC) was given to the other. The dialysate levels of 5-HT in the frontal cortex (FX_C) expressed as % of corresponding pre-injection baseline, are shown in Figure.

Results:

NAD 299 (0.3 mg/kg SC) administered 60 minutes after citalopram (5 mg/kg SC), strongly potentiated the 5-HT-elevating action of citalopram vs. controls (receiving citalopram + NaCl).

Conclusions

The data presented in the Figure show that *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate (NAD 299) displays potent 5 HT_{1A} autoreceptor blocking properties, as evidenced by its ability to antagonize increases in endogenous agonist (5-HT) tonus at the 5-HT_{1A} autoreceptors, as induced by citalopram and thereby potentiating the citalopram-induced 5-HT elevation in forebrain areas. Through its blocking of $5HT_{1A}$ autoreceptors, *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate may become clinically useful in the treatment of 5-HT mediated disorders, particularly mood disorders.

The following non-limiting Example serves to illustrate the present invention.

Example

A suitable pharmaceutical composition comprising a first component (a) and a second component (b) in a single dosage form include the following:

Composition	mg/tablet
Active drug component (a)	5
Active drug component (b)	20
Microcrystalline cellulose	100
Corn starch	40
Povidone	4
Water	50
Sodium starch glycolate	8
Magnesium stearate	1

CLAIMS

1. A composition comprising of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof.

2. The composition according to claim 1 wherein the second component (b) is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile in racemic form.

3. The composition according to claim 1 wherein the second component (b) is (+)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile.

4. Use of the composition according to any one of claims 1-3 for the manufacture of a medicament for the treatment of 5-HT mediated disorders.

5. The use according to claim 4 for the manufacture of a medicament for the treatment of affective disorders.

6. The use according to claim 5 for the manufacture of a medicament for the treatment of mood disorders.

7. The use according to claim 6 for the manufacture of a medicament for the treatment of depression.

8. A method for the treatment of 5-HT mediated disorders by administering to a patient suffering therefrom the composition defined in any one of claims 1-3.

9. The method according to claim 8 for the treatment of affective disorders.

10. The metod according to claim 9 for the treatment of mood disorders.

11. The metod according to claim 10 for the treatment of depression.

12. A method of improving the onset of therapeutic action by concomitant administration of a composition defined in any one of claims 1-3.

13. A pharmaceutical formulation wherein the active ingredients are those in the composition defined in any one of claims 1-3, optionally in association with adjuvants, excipients and/or inert carriers.

14. A pharmaceutical formulation according to claim 13 wherein the first component (a) is concomitantly administered with the second component (b).

15. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of 5-HT mediated disorders.

16. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of affective disorders.

17. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of mood disorders.

18. A pharmaceutical formulation according to any one of claims 13-14 for use in the treatment of depression.

19. A process for the preparation of the composition according to any one of claims

1-3 whereby the first component (a) is incorporated into the same pharmaceutical formulation as the second component (b).

20. A process for the preparation of the composition according to any one of claims 1-3 whereby the first component (a) is in a one pharmaceutical formulation and is combined with the second component (b) is in a different pharmaceutical formulation.

21. A kit containing a dosage unit of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, optionally with instructions for use.

AMENDED CLAIMS

[received by the International Bureau on 15 February 2000 (15.02.00);
original claims 8,13 and 20 amended; remaining claims unchanged (3 pages)]

1. A composition comprising of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof.

2. The composition according to claim 1 wherein the second component (b) is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile in racemic form.

3. The composition according to claim 1 wherein the second component (b) is (+)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile.

4. Use of the composition according to any one of claims 1-3 for the manufacture of a medicament for the treatment of 5-HT mediated disorders.

5. The use according to claim 4 for the manufacture of a medicament for the treatment of affective disorders.

6. The use according to claim 5 for the manufacture of a medicament for the treatment of mood disorders.

7. The use according to claim 6 for the manufacture of a medicament for the treatment of depression.

8. The use according to claim 4 in the manufacture of a medicament in the prevention or in the treatment of urinary incontinence.

9. A method for the treatment of 5-HT mediated disorders by administering to a patient suffering therefrom the composition defined in any one of claims 1-3.

10. The method according to claim 9 for the treatment of affective disorders.

11. The metod according to claim 10 for the treatment of mood disorders.

12. The metod according to claim 11 for the treatment of depression.

13. A method according to claim 9 for the prevention or the treatment of urinary incontinence.

14. A method of improving the onset of therapeutic action by concomitant administration of a composition defined in any one of claims 1-3.

15. A pharmaceutical formulation wherein the active ingredients are those in the composition defined in any one of claims 1-3, optionally in association with adjuvants, excipients and/or inert carriers.

16. A pharmaceutical formulation according to claim 15 wherein the first component (a) is concomitantly administered with the second component (b).

17. A pharmaceutical formulation according to any one of claims 15-16 for use in the treatment of 5-HT mediated disorders.

18. A pharmaceutical formulation according to any one of claims 15-16 for use in the treatment of affective disorders.

19. A pharmaceutical formulation according to any one of claims 15-16 for use in the treatment of mood disorders.

20. A pharmaceutical formulation according to any one of claims 15-16 for use in the treatment of depression.

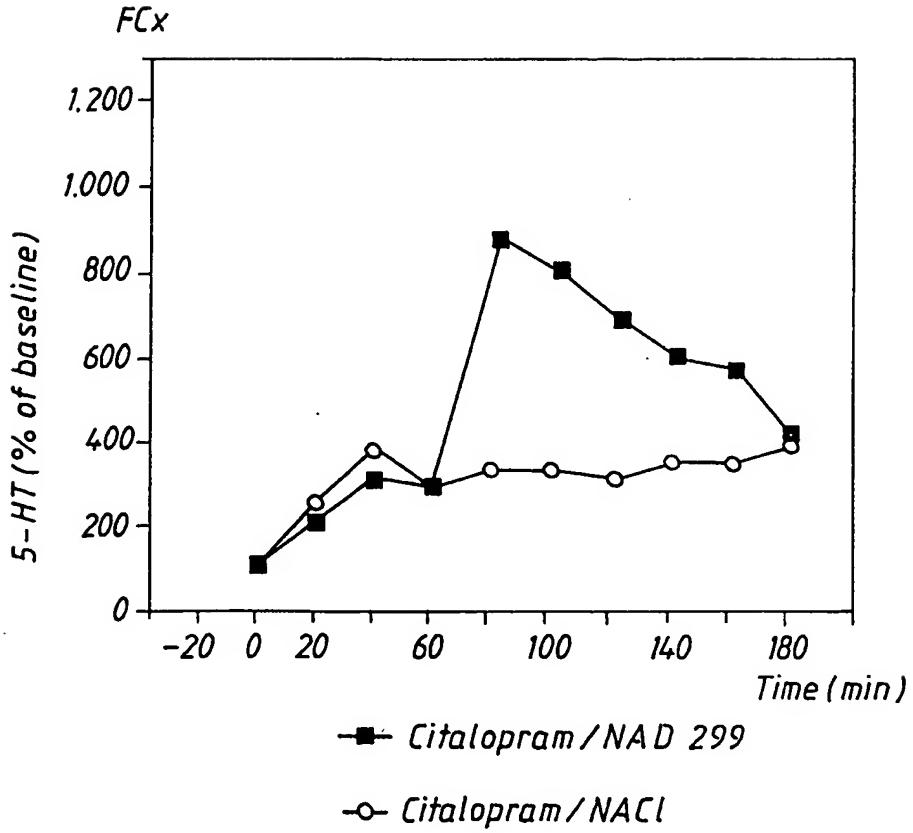
21. A pharmaceutical formulation according to any one of claims 15-16 for use in the treatment of urinary incontinence.

22. A process for the preparation of the composition according to any one of claims 1-3 whereby the first component (a) is incorporated into the same pharmaceutical formulation as the second component (b).

23. A process for the preparation of the composition according to any one of claims 1-3 whereby the first component (a) is in a one pharmaceutical formulation and is combined with the second component (b) is in a different pharmaceutical formulation.

24. A kit containing a dosage unit of a first component (a) which is *(R)*-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate and a dosage unit of a second component (b) which is 1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile, as the racemate or an enantiomer thereof, in the form of the free base, or a pharmaceutically acceptable salt and/or solvate thereof, optionally with instructions for use.

Fig.


FCx
1.200
1.000
800
600
400
200
0
5-HT (% of baseline)
-20
0
20
60
100
140
180
Time (min)
Citalopram / NAD 299
Citalopram / NACl

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01598

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9633710 A1 (ASTRA AKTIEBOLAG), 31 October 1996 (31.10.96) -- --------	1-7,13-21

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 1999	22 -01- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/01598

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 8-12
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see Rule 39.1

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/01598

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633710 A1	31/10/96	AU 696356 B	10/09/98
		AU 5520296 A	18/11/96
		BR 9608252 A	04/05/99
		CA 2218181 A	31/10/96
		CZ 9703356 A	17/06/98
		EP 0807241 A	19/11/97
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		NO 973445 A	25/07/97
		NO 974921 A	18/12/97
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